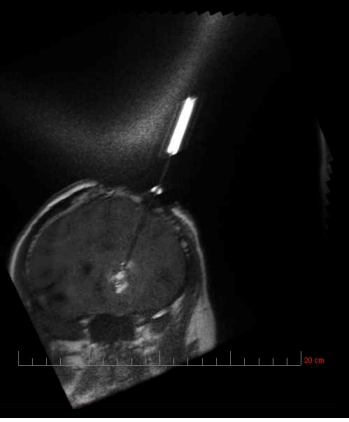
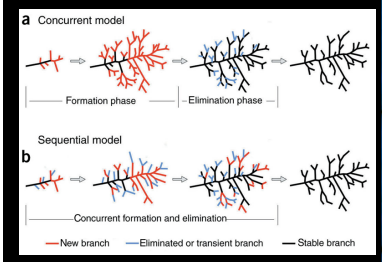
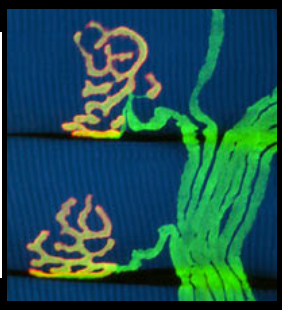
Gene therapy for the Nervous System



I fattori neurotrofici





La sopravvivenza dei motoneuroni delle corna anteriori del midollo spinale dipende strettamente dalla produzione di fattori neurotrofici da parte del muscolo innervato: solo i neuroni che raggiungono il muscolo bersaglio durante lo sviluppo sopravvivono, mentre gli altri vanno in contro ad un processo di apoptosi.

I fattori neurotrofici nell'adulto controllano la sintesi proteica e la sintesi di neurotrasmettitori.

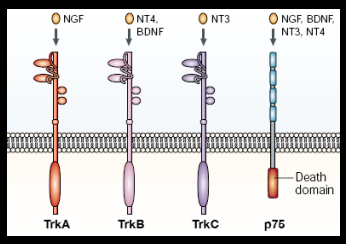
Families of neurotrophic factors

Box 1 | Haploinsufficiency of neurotrophins

NGF$^{+/-}$ mice
- Decreased cholinergic innervation of the hippocampus[15]
- Deficiency in memory acquisition and retention[15]
- Loss of neurons of the peripheral nervous system[121]

BDNF$^{+/-}$ mice
- Hyperphagia, obesity[16–18]
- Impairment of long-term potentiation[19,20,122]
- Elevated striatal dopamine levels[123]
- Loss of mechanosensitivity[124]
- Loss of neurons of the peripheral nervous system[125,126]

NT3$^{+/-}$ mice
- Deficient amygdala KINDLING activity[127]
- Cardiovascular defects[128]
- Reduced mechanoreceptors[129]
- Loss of neurons of the peripheral nervous system[130]

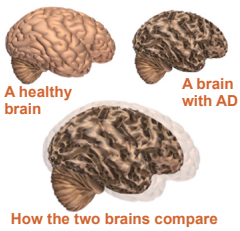


1. Neurotrophins: NGF, BDNF, NT-3, NT-4
2. GDNF: GDNF, neurturin (NTN), artemin (ART), persephin (PSP)
3. CNTF/LIF

R. Levi Montalcini

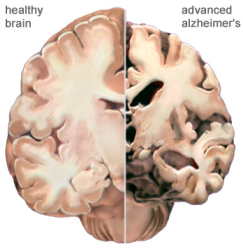
Alzheimer's Disease

7% of people over 65, 40% over 80



How the two brains compare

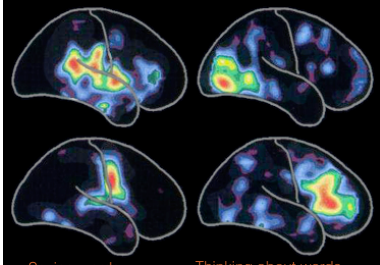
Dramatic loss of cholinergic neurons



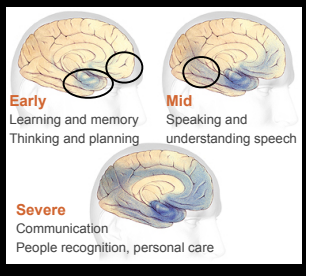
- The cortex shrivels up, damaging areas involved in thinking, planning and remembering.
- Shrinkage is especially severe in the hippocampus, an area of the cortex that plays a key role in formation of new memories.
- Ventricles (fluid-filled spaces within the brain) grow larger.

AD progression in the brain

Hearing words | Reading words



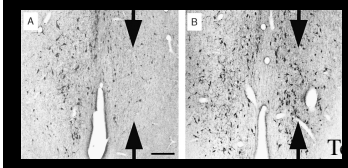
Saying words | Thinking about words



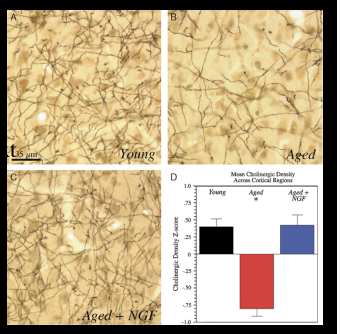
- **Earliest Alzheimer's** – changes may begin 20 years or more before diagnosis.
- **Mild to moderate Alzheimer stages** – generally last from 2 - 10 years.
- **Severe Alzheimer's** – may last from 1 - 5 years.

No effective therapy available able to modify disease progression

NGF therapy for AD



NGF prevents cholinergic neuronal death in rodents and primates and restores cortical cholinergic terminal density in aged primates (dogma revolution: growth factor biology era!!)

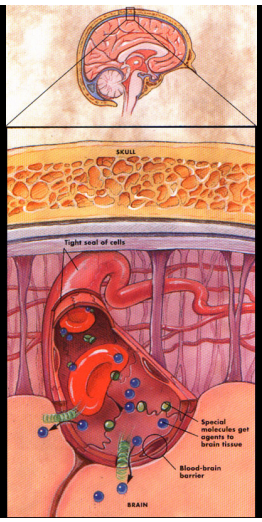


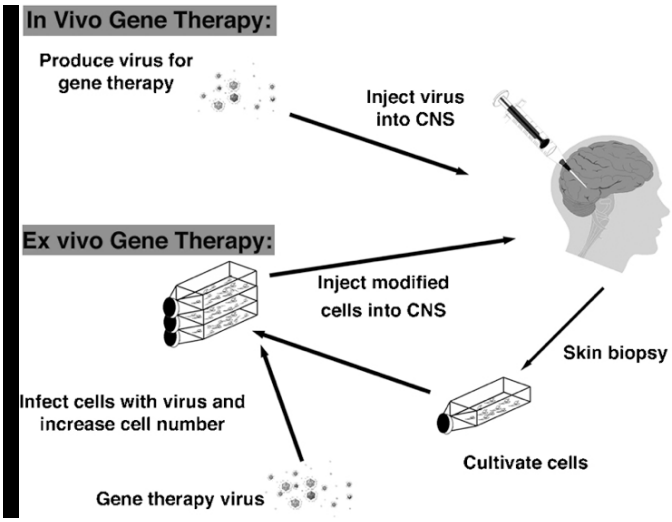
- protection of basal forebrain cholinergic neurons after axotomy
- reversion of age-related atrophy
- improved learning and memory

→ INITIATION OF CLINICAL TRIALS

- NGF is relatively large and polar molecule compared with most drugs
- NGF does not cross the BBB: it requires CNS administration
- Adverse effects arising from cells (other than cholinergic neurons) expressing NGF receptors: pain (stimulation of dorsal root ganglion nociceptive neurons), weight loss, sympathetic axon sprouting in the cerebral vasculature, Schwann cell proliferation.

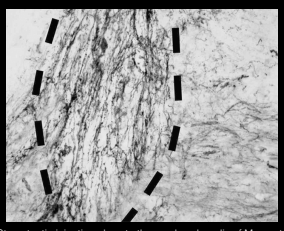
GENE DELIVERY





Ex Vivo NGF Gene Therapy for AD

- Skin biopsy to generate primary fibroblast cultures
- MLV-NGF vector to secrete hNGF within a range of 50-75 ng/10^6 cells/d (3 dose cohorts enrolled)
- Initially subjects were treated in a sedated but wakeful state but 2 subjects moved during injection resulting in intraparenchymal hemorrhage. Subsequently, all subjects underwent general anesthesia.

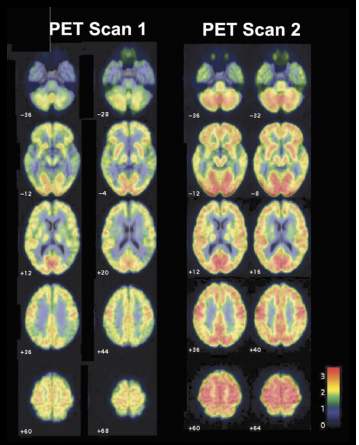


Stereotactic injection close to the nucleus basalis of Meynert, from where cholinergic neurons project toward the whole cortex

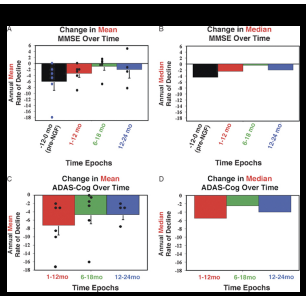
- One individual died 5 weeks post NGF delivery: cholinergic axons robustly extended toward the site of NGF gene transfer

Nat Med. 2005;11:551–555

- Mean follow-up: 3.5 years
- No long-term adverse effects
- Serial MRI and PET scans: statistically significant increase in cortical glucose uptake after 6-8 months (AD normally results in a steady decline)



- Cognitive tests not conclusive but suggestive of possible reduction in rate of decline (Mini-Mental Status Examination and AD Assessment Scale-Cognitive sub-component)

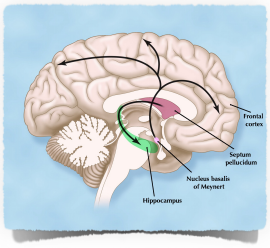


Conclusions

1. NGF can be delivered safely to the brain over an extended period using gene delivery but needs general anesthesia or deep sedation
2. Degenerating cholinergic neurons of the human brain exhibit trophic response to NGF
3. Broad cortical regions demonstrate enhance glucose metabolism
4. Larger, controlled, blinded clinical trials of NGF delivery are warranted

Stereotactic gene delivery of AAV2-NGF for AD

Sangamo BioSciences announces positive data from the Phase 1 clinical trial of CERE-110 (AAV-NGF), a gene therapy approach designed to deliver NGF for AD treatment. This novel product was developed by Ceregene, which was recently acquired by Sangamo.



Results

AAV2-NGF was safe and well-tolerated for 2 years. Positron emission tomographic imaging and neuropsychological testing showed no evidence of accelerated decline. Brain autopsy tissue confirmed long-term, targeted, gene-mediated NGF expression and bioactivity.

Conclusions

This trial provides important evidence that bilateral stereotactic administration of AAV2-NGF to the nucleus basalis of Meynert is feasible, well-tolerated, and able to produce long-term, biologically active NGF expression, supporting the initiation of multicenter, double-blind, sham-surgery-controlled trial.

MAY 15, 2014

JAMA Neurology | Original Investigation

Adeno-Associated Viral Vector (Serotype 2)–Nerve Growth Factor for Patients With Alzheimer Disease

A Randomized Clinical Trial

Michael S. Rafii, MD, PhD; Mark H. Tuszynski, MD, PhD; Ronald G. Thomas, PhD; David Barba, MD; James B. Brewer, MD, PhD; Robert A. Rissman, PhD; Joao Siffert, MD; Paul S. Aisen, MD; for The AAV2-NGF Study Team

IMPORTANCE Nerve growth factor (NGF) is an endogenous neurotrophic factor that prevents the death and augments the functional state of cholinergic neurons of the basal forebrain, a cell population that undergoes extensive degeneration in Alzheimer disease (AD).

OBJECTIVE To determine whether stereotactically guided intracerebral injections of adeno-associated viral vector (serotype 2)–nerve growth factor (AAV2-NGF) are well tolerated and exhibit preliminary evidence of impact on cognitive decline in mild to moderate AD–associated dementia.

DESIGN, SETTING, AND PARTICIPANTS In a multicenter phase 2 trial, 49 participants with mild to moderate AD were randomly assigned in a 1:1 ratio to receive stereotactically guided intracerebral injections of AAV2-NGF or sham surgery. Participants were enrolled between November 2009 and December 2012. Analyses began in February 2015. The study was conducted at 10 US academic medical centers. Eligibility required a diagnosis of mild to moderate dementia due to AD and individuals aged 55 to 80 years. A total of 39 participants did not pass screening, the most common reason was Mini-Mental State Examination scores below cutoff. Analyses were intention-to-treat.

INTERVENTIONS Stereotactically guided intracerebral injections of AAV2-NGF into the nucleus basalis of Meynert of each hemisphere or sham surgery.

MAIN OUTCOMES AND MEASURES Change from baseline on the Alzheimer Disease Assessment Scale–cognitive subscale at month 24.

RESULTS Among 49 participants, 21 (43%) were women, 42 (86%) self-identified as white, and the mean (SD) age was 68 (6.4) years. AAV2-NGF was safe and well-tolerated through 24 months. No significant difference was noted between the treatment group and placebo on the primary outcome measure, the Alzheimer Disease Assessment Scale–cognitive subscale (mean [SD] score, 14.52 [4.66] vs 9.11 [4.65], $P = .17$).

CONCLUSIONS AND RELEVANCE This multicenter randomized clinical trial demonstrated the feasibility of sham-surgery–controlled stereotactic gene delivery studies in patients with AD. AAV2-NGF delivery was well-tolerated but did not affect clinical outcomes or selected AD biomarkers. Pathological confirmation of accurate gene targeting is needed.

TRIAL REGISTRATION clinicaltrials.gov Identifier NCT00876863

Table 3. Change on Outcome Measures at 24 mo (N = 49)

Outcome Measure[a]	Mean Change (95% CI) Placebo Group (n = 23)	Treatment Group (n = 26)	P Value
ADAS-Cog 11[b]	9.11 (4.46 to 13.57)	14.52 (9.86 to 19.18)	.17
CDR-SOB	2.81 (1.34 to 4.28)	4.75 (3.20 to 6.30)	.09
mCGIC	5.33 (5.06 to 5.60)	5.59 (5.26 to 5.92)	.21
MMSE	−4.17 (−6.84 to 1.50)	−6.18 (−8.36 to 4.00)	.16
NPI	9.18 (−0.71 to 19.07)	6.61 (1.85 to 11.37)	.95
ADCS-ADL	−12.94 (−22.13 to 3.75)	−17.65 (−24.49 to 10.81)	.61

Abbreviations: ADAS-Cog 11, Alzheimer's Disease Assessment Scale–cognitive subscale; ADCS-ADL, Alzheimer Disease Cooperative Study–Activities of Daily Living; CDR-SOB, Clinical Dementia Rating–sum of boxes; mCGIC, modified Clinical Global Impression of Change; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory.

[a] In almost all outcome measures, there was a trend toward worsening in the treatment arm.

[b] There was no statistical difference in ADAS-Cog 11 at 24 months between treatment and placebo arms. Mean (SD) change was 14.52 (4.66) for treatment vs 9.11 (4.65) for the placebo group ($P = .17$).

JAMA Neurol. doi:10.1001/jamaneurol.2018.0233
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EDITORIAL

Gene Therapy in Alzheimer Disease—It May Be Feasible, but Will It Be Beneficial?

Lawrence S. Honig, MD, PhD

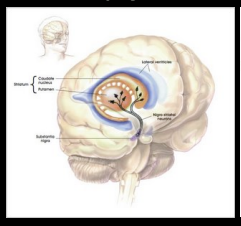
This study provides a lesson on historical controls because it was performed after an open-label phase 1 trial on 10 individuals seemed to show stability and decreased cognitive and functional decline compared with historical controls.

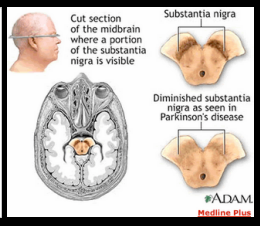
The fact that no benefit was evident in this randomized, double-blind phase 2 study emphasizes the lack of scientific validity for open-label comparisons with historical controls in clinical trials. The reasons why treatments so often appear beneficial in comparisons with untreated historical controls are well-known:

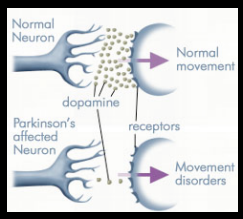
(1) individuals in a treatment trial are from a different population sample than those in observational studies, are often highly motivated, and receive better symptomatic and general treatments

(2) historical controls are from an earlier period, and given a secular trend toward earlier diagnosis and ascertainment earlier in the disease course, current trial participants usually appear to have more stable disease status than historical controls did. This may be relevant to other recent restorative therapy trials with controversial analyses in which historical controls were used as evidence of possible efficacy.

Gene therapy for Parkinson Disease



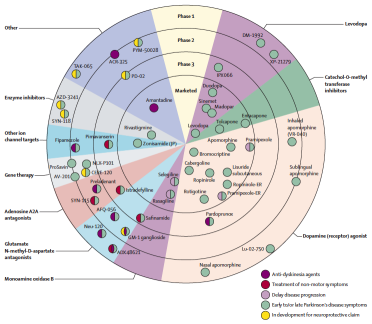




- Rigidity — Arms and legs become stiff and hard to move
- Tremors — Rapid shaking of the hands, arms or legs
- Slowed Movements — Difficulty starting or completing movements, called bradykinesia
- Impaired Balance — Lack of balance or difficulty adjusting to sudden changes in position

Current therapies for PD

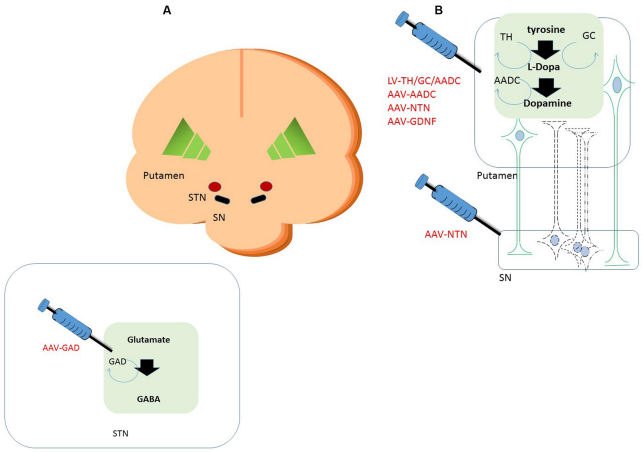
- Replacement therapy levo-dopa + carbidopa: long-term complications limiting the dose
- Deep brain stimulation: technically complex
- Human fetal mesencephalic cell transplantation: double-blind controlled trials disappointing



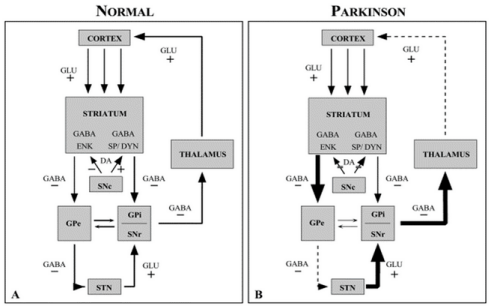
Gene therapy for PD

- Enhancement of DA synthesis
- Delivery of neurotrophic factors (neurturin)
- Interference with aberrant protein aggregation
- AAV-GAD: conversion of the subthalamic nucleus in an inhibitory rather than an excitatory structure

Brain targets in PD gene therapy



AAV-GAD Background & Rationale



In PD, loss of DA projections from the SN to the striatum results in overactivity of the subthalamic nucleus.

The subthalamic nucleus sends excitatory projections to the internal part of globus pallidus and the pars reticulata of the SN, which in turn inhibits motor output.

AAV-GAD Background & Rationale

- Adeno-associated virus (AAV) vectors can yield safe, stable gene transfer in the adult brain (Kaplitt, et. al. Nat. Gen. 8:148-154,1994)
- GAD is the rate-limiting enzyme in synthesis of GABA
- GABA infusion in STN reduces firing and improves symptoms transiently (Levy, et. al., Brain 124:2105-2118, 2001)
- AAV-GAD improves motor function and normalizes motor circuits in rodent and primate PD models (Luo, et. al., Science 298:425-429,2002; Emborg, et. al., J Cereb Blood Flow Metab 27:501-509, 2007)

Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial

Michael G Kaplitt, Andrew Feigin, Chengke Tang, Helen L Fitzsimons, Paul Mattis, Patricia A Lawlor, Ross J Bland, Deborah Young, Kristin Strybing, David E Idelberg, Matthew J During

Lancet 2007; 369: 2097–105

- 12 patients
- 5x10^9-5x10^10 AAV2-GAD particles infused unilaterally

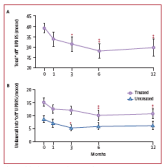
Results

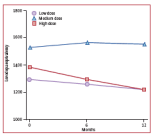
No adverse events related to the gene therapy

Clinical improvement in motor rating

Changes of daily dose of dopaminergic medication

Reduction in glucose metabolism of the thalamus in the operated hemisphere





Two patients showed evidence of substantial anti-AAV2 immunity but no changes over time, suggesting that vector infusion did not induce immunity against AAV2

Surprising findings:

- bilateral improvement after unilateral therapy
- improvement in best on-medication function

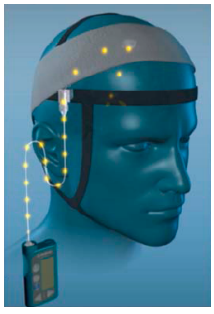
Concerns:

- absence of sham-operated control group
- the excitatory role of the subthalamic nucleus suggests its role in learning: what might be the long-term effect of converting this nucleus from an excitatory to an inhibitory structure?

NEUROLOGIX

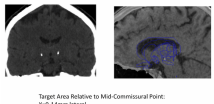
- The primary objective of the Phase 2 study is to evaluate the clinical antiparkinsonian efficacy of rAAV-GAD, administered bilaterally into the subthalamic nucleus of 20 subjects with advanced PD, for comparison to 20 sham-operated PD controls at 6 months after the procedure
- The secondary objectives are
  - To evaluate the safety of rAAV-GAD administered to bilateral subthalamic nuclei through 12 months after the procedure
  - To assess the outcomes of rAAV-GAD administration on PD disability, activities of daily living, motor fluctuations, dyskinesias, and quality of life assessments through 12 months after the procedure
  - To evaluate metabolic activity related to PD measured by FDG-PET through 12 months after the procedure

- With the patient under local anesthesia, the neurosurgeon will drill burr holes on both sides of the skull
- A stereotactic frame will be used to place small catheters in the subthalamic nucleus, after targeting based on presurgical CT scan or MRI; the planning procedure is comparable to DBS
- Once the catheters are in place, the burr holes will be covered with a special capping system and the patient will be transferred to the recovery room for infusion of the study agent or saline



- The infusion system was codeveloped by Neurologix and Medtronic and is approved for use in this procedure
  - It should be noted that this system is investigational and is not approved for other uses
- Infusion takes place in the recovery room for 150 minutes
- Imaging is used to verify placement of the catheter
- CT and MRI scans are used for safety measurements at 24 and 48 hours, respectively, before the patient is released from the hospital

Blinded Catheter Tip Localization



Target Area Relative to Mid-Commissural Point:
X=9-14mm lateral
Y=2mm anterior-5mm posterior
Z=1mm dorsal-7mm ventral

(Standard DBS tip coordinates in postero-ventral STN:
X=12mm lateral, Y=3.5mm posterior, Z=4mm ventral)

Medtronic
When Life Depends on Medical Technology

7 participating centers in the United States

Phase 2 Trial Sites

Site	Principal Investigator	Neurosurgeon
Henry Ford	Peter Lewitt, MD	Jason Schwalb, MD
Massachusetts General Hospital	Alice Flaherty, MD	Emad Eskandar, MD
The Ohio State University	Sandra Kostyk, MD, PhD	Atom Sarkar, MD, PhD Ali Rezai, MD
Stanford University	Kathleen Poston, MD, PhD	Jaimie Henderson, MD
University of Colorado	Maureen Leehey, MD	Steven Ojemann, MD
University of Rochester	Roger Kurlan, MD	Jason Schwalb, MD
Wake Forest University	Mustafa Siddiqui, MD	Stephen Tatter, MD, PhD
The Feinstein Institute (Centralized PET imaging)	Andrew Feigin, MD, PhD	-------

Each surgeon completed a minimum of 3 surgeries

AAV2-GAD into STN produces motor improvements for at least a year

Long-term follow-up of a randomized AAV2-*GAD* gene therapy trial for Parkinson's disease

Martin Niethammer,[1] Chris C. Tang,[1] Peter A. LeWitt,[2] Ali R. Rezai,[3] Maureen A. Leehey,[4] Steven G. Ojemann,[5] Alice W. Flaherty,[6] Emad N. Eskandar,[3,4] Sandra K. Kostyk,[2] Atom Sarkar,[7] Mustafa S. Siddiqui,[8] Stephen B. Tatter,[9] Jason M. Schwalb,[9] Kathleen L. Poston,[10,11] Jaimie M. Henderson,[12] Roger M. Kurlan,[13] Irene H. Richard,[14] Christine V. Sapan,[14] David Eidelberg,[1] Matthew J. During,[3,15] Michael G. Kaplitt,[16] and Andrew Feigin[1]

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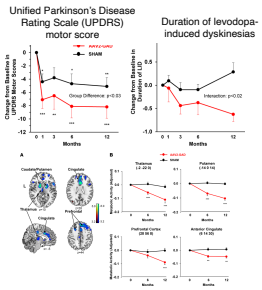
CONCLUSION. These findings show that clinical benefits after gene therapy with STN AAV2-*GAD* in PD patients persist at 12 months.

45 patients
bilateral injection
control: sham surgery

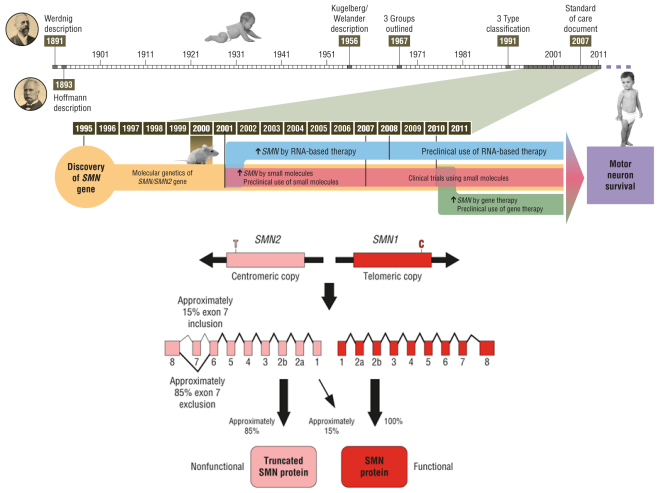


MEIRAGTx pipeline

PRODUCT CANDIDATE	INDICATION	PRECLINICAL	PHASE 1/2	PHASE 3	
Ocular Programs					
AAV-RPGR	X-linked RP (*RPGR*)*				janssen
AAV-RPE65	RPE65-Deficiency (*RPE65*)				
AAV-CNGB3	Achromatopsia (*CNGB3*)*				janssen
AAV-CNGA3	Achromatopsia (*CNGA3*)*				janssen
Neurodegenerative Diseases Program					
AAV-GAD	Parkinson's (*GAD*)				
AAV-UPF1	ALS (*UPF1*)				
Salivary Gland Programs					
AAV-AQP1	Xerostomia (*hAQP1*)				
AAV-AQP1	Sjogren's (*hAQP1*)				

*Co-development program with Janssen Pharmaceuticals pursuant to a collaboration agreement.

MEIRAGTx Phase 3 trial for PD to be started in 2021



SMA severity depends on SMN2 copy number

SMA Types: A Devastating Disease

	TYPE 1	TYPE 2	TYPE 3	TYPE 4
SMN2 Copy Number	Two	Three or Four	Three or Four	Four to Eight
Onset	Before 6 Months	6-18 Months	Early childhood to early adulthood (juvenile)	Adulthood (20s-30s) usually after 30
Incidence per Live Birth	Approximately 60%	Approximately 27%	Approximately 13%	Uncommon; limited information available
Developmental Milestones	• Will never be able to sit without support • Difficulty breathing & swallowing • Can't crawl/will never walk	• Will never be able to walk or stand without support	• Stand alone and walk but may lose ability to walk in 30s-40s	• Stand alone and walk but may lose ability to walk in 30s-40s (Same as Type 3)
Survival	• <10% Event free* by two years of age	• 68% alive at age 25	• Normal	• Normal

*Event = Death or ≥16-hr/day ventilation continuously for ≥ 2 wks, in the absence of an acute reversible illness

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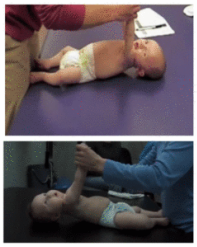
Children with SMA Type 1 Never Sit Unassisted

The Natural History of SMA Type 1 is marked by the inability to achieve or maintain developmental milestones



Disease Characteristics

- Disease onset <6 months
- Hypotonia and weakness
- Bulbar muscle weakness
- Difficulty breathing and swallowing
- Inexorable progression to nutritional failure
- Inexorable progression to respiratory failure

Developmental Milestone Prognosis

- Progressive decline in motor function soon after birth
- Rapid loss of any early milestones (e.g. head control, hands to mouth)
- Will never be able to sit unassisted
- Will never be able to roll
- Will never be able to crawl, stand, or walk

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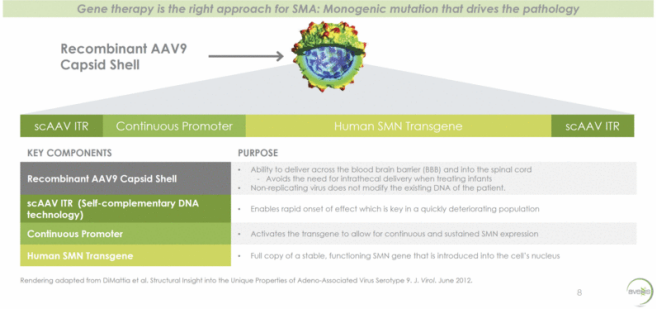
GT for SMA: AAV9-SMN1

Our Solution: AVXS-101

An Innovative Treatment Approach for SMA

Gene therapy is the right approach for SMA: Monogenic mutation that drives the pathology



KEY COMPONENTS	PURPOSE
Recombinant AAV9 Capsid Shell	• Ability to deliver across the blood brain barrier (BBB) and into the spinal cord – Avoids the need for intrathecal delivery when treating infants • Non-replicating virus does not modify the existing DNA of the patient.
scAAV ITR (Self-complementary DNA technology)	• Enables rapid onset of effect which is key in a quickly deteriorating population
Continuous Promoter	• Activates the transgene to allow for continuous and sustained SMN expression
Human SMN Transgene	• Full copy of a stable, functioning SMN gene that is introduced into the cell's nucleus

Rendering adapted from DiMattia et al. Structural Insight into the Unique Properties of Adeno-Associated Virus Serotype 9. J. Virol. June 2012.

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The NEW ENGLAND JOURNAL of MEDICINE

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

Jerry R. Mendell, M.D., Samiah Al-Zaidy, M.D., Richard Shell, M.D., W. Dave Arnold, M.D., Louise R Rodino-Klapac, Ph.D., Thomas W. Prior, Ph.D., Linda Lowes, P.T., Ph.D., Lindsay Alfano, D.P.T., Katherine Berry, P.T., Kathleen Church, M.S.W., John T. Kissel, M.D., Sukumar Nagendran, M.D., James L'Italien, Ph.D., Douglas M. Sproule, M.D., Courtney Wells, B.S., Jessica A. Cardenas, Ph.D., Marjet D. Heitzer, Ph.D., Allan Kaspar, Ph.D., Sarah Corcoran, B.S., Lyndsey Braun, B.S., Shibi Likhite, Ph.D., Carlos Miranda, Ph.D., Kathrin Meyer, Ph.D., K.D. Foust, Ph.D., Arthur H.M. Burghes, Ph.D., and Brian K. Kaspar, Ph.D. et al.

Feedback

RESULTS As of the data cutoff on August 7, 2017, all 15 patients were alive and event-free at 20 months of age, as compared with a rate of survival of 8% in a historical cohort. In the high-dose cohort, a rapid increase from baseline in the score on the CHOP INTEND scale followed gene delivery, with an increase of 9.8 points at 1 month and 15.4 points at 3 months, as compared with a decline in this score in a historical cohort. Of the 12 patients who had received the high dose, 11 sat unassisted, 9 rolled over, 11 fed orally and could speak, and 2 walked independently. Elevated serum aminotransferase levels occurred in 4 patients and were attenuated by prednisolone.

Phase I, sc-AAV9

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

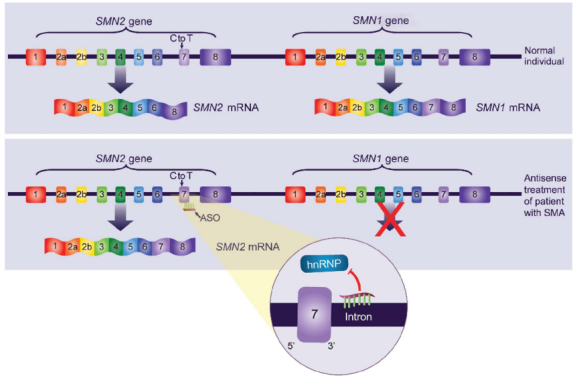
27 March 2020
EMA/163207/2020
Media and Public Relations

Press release

New gene therapy to treat spinal muscular atrophy

EMA has recommended granting a conditional marketing authorisation in the European Union for the gene therapy Zolgensma (onasemnogene abeparvovec) to treat babies and young children with spinal muscular atrophy (SMA), a rare and often fatal genetic disease that causes muscle weakness and progressive loss of movement.

SPINRAZA® (nusinersen) injection 12 mg/5 mL



Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

Richard S. Finkel, M.D., Eugenio Mercuri, M.D., Ph.D., Basil T. Darras, M.D., Anne M. Connolly, M.D., Nancy L. Kuntz, M.D., Janbernd Kirschner, M.D., Claudia A. Chiriboga, M.D., M.P.H., Kayoko Saito, M.D., Ph.D., Laurent Servais, M.D., Ph.D., Eduardo Tizzano, M.D., Ph.D., Haluk Topaloglu, M.D., Már Tulinius, M.D., Ph.D., Jacqueline Montes, P.T., Ed.D., N.C.S., Allan M. Glanzman, P.T., D.P.T., P.C.S., Kathie Bishop, Ph.D., Z. John Zhong, Ph.D., Sarah Gheuens, M.D., Ph.D., C. Frank Bennett, Ph.D., Eugene Schneider, M.D., Wildon Farwell, M.D., M.P.H., and Darryl C. De Vivo, M.D. et al., for the ENDEAR Study Group*

Feedback

The NEW ENGLAND JOURNAL of MEDICINE

RESULTS In the interim analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (21 of 51 infants [41%] vs. 0 of 27 [0%], P<0.001), and this result prompted early termination of the trial. In the final analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]), and the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; P=0.005). The likelihood of overall survival was higher in the nusinersen group than in the control group (hazard ratio for death, 0.37; P=0.004), and infants with a shorter disease duration at screening were more likely than those with a longer disease duration to benefit from nusinersen. The incidence and severity of adverse events were similar in the two groups.

November 2, 2017

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 377;18 NEJM.ORG NOVEMBER 2, 2017

EDITORIAL

The Dilemma of Two Innovative Therapies for Spinal Muscular Atrophy

Ans T. van der Ploeg, M.D., Ph.D.

- Different study designs, hard to compare results
- scAAV9 gene therapy may require a single i.v. infusion (difficult to repeat), whereas nusinersen requires lifelong repetitive intrathecal treatment
- As the children grow, the phenotype may expand to affect other organs and tissues (do scAAV9 and antisense oligonucleotides target other cell types?).
- Neither therapy currently provides a cure. One option may be to start treatment earlier; the NURTURE study (ClinicalTrials.gov number, NCT02386553) is currently investigating the effect of nusinersen in presymptomatic patients. Another option is to combine the two treatments.
- An important constraint is the high anticipated cost of $750,000 for a course of nusinersen during the first year of therapy

scAAV9 gene therapy: 15 patients (3 low dose, 12 high dose)

In the high-dose group 9 patients were able to sit without support for at least 30 seconds, and 2 were able to crawl, pull to stand, and walk independently and 7 patients did not require ventilatory support.

Nusinersen: 122 infants with onset of symptoms at 6 months of age or younger.

Of the infants who achieved motor milestones (51%), only 8% could sit independently and 1% could stand. 39% of the infants in the nusinersen group and 68% in the control group had died or received permanent assisted ventilation.

Best results in patients who started treatment within 13 weeks after disease onset.

Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy

Eugenio Mercuri, M.D., Ph.D., Basil T. Darras, M.D., Claudia A. Chiriboga, M.D., M.P.H., John W. Day, M.D., Ph.D., Craig Campbell, M.D., Anne M. Connolly, M.D., Susan T. Iannaccone, M.D., Janbernd Kirschner, M.D., Nancy L. Kuntz, M.D., Kayoko Saito, M.D., Ph.D., Perry B. Shieh, M.D., Ph.D., Már Tulinius, M.D., Ph.D., Elena S. Mazzone, D.P.T., Jacqueline Montes, P.T., Ed.D., Kathie M. Bishop, Ph.D., Qingqing Yang, M.S., Richard Foster, M.Sc., Sarah Gheuens, M.D., Ph.D., C. Frank Bennett, Ph.D., Wildon Farwell, M.D., M.P.H., Eugene Schneider, M.D., Darryl C. De Vivo, M.D., and Richard S. Finkel, M.D. et al., for the CHERISH Study Group*

Feedback

RESULTS In the prespecified interim analysis, there was a least-squares mean increase from baseline to month 15 in the HFMSE score in the nusinersen group (by 4.0 points) and a least-squares mean decrease in the control group (by −1.9 points), with a significant between-group difference favoring nusinersen (least-squares mean difference in change, 5.9 points; 95% confidence interval, 3.7 to 8.1; P<0.001). This result prompted early termination of the trial. Results of the final analysis were consistent with results of the interim analysis. In the final analysis, 57% of the children in the nusinersen group as compared with 26% in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points (P<0.001), and the overall incidence of adverse events was similar in the nusinersen group and the control group (93% and 100%, respectively).

CONCLUSIONS Among children with later-onset SMA, those who received nusinersen had significant and clinically meaningful improvement in motor function as compared with those in the control group. (Funded by Biogen and Ionis Pharmaceuticals; CHERISH ClinicalTrials.gov number, NCT02292537.)

Phase III, repeated intrathecal administration

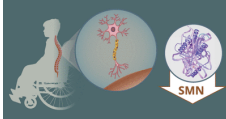
Nusinersen in later-onset spinal muscular atrophy

Long-term results from the phase 1/2 studies

Neurology® 2019;92:e2492-e2506. doi:10.1212/WNL.0000000000007527

Is long-term nusinersen effective for later-onset SMA?

Spinal muscular atrophy (SMA) is characterized by progressive muscular atrophy and weakness.



Analysis of the long-term efficacy of nusinersen on SMA is lacking.

Homozygous deletions or mutations in the **survival motor neuron 1 (*SMN1*)** gene cause decreased functional **SMN protein**.

Nusinersen has been shown to effectively increase full-length SMN protein levels.

Study Question

What is the long-term effectiveness and safety of nusinersen in children with later-onset SMA?

Integrated analysis

28 children (Aged: 2–15 years at enrollment)

SMA Type II: n = 11; SMA Type III: n = 17

Nusinersen (mg)

Phase 1b/2a study (253 days) — 3, 6, 9, 12

Extension study (715 days) — 12

Mean change from baseline over ~3 years of treatment

Motor assesment	SMA Type II	SMA Type III
Hammersmith Functional Motor Scale–Expanded score	+10.8 points	+1.8 points
Upper Limb Module score	+4.0 points	NR*
Six-Minute Walk Test distance	NR*	+92.0 points

No children discontinued treatment due to adverse events.

*Not reported

Long-term nusinersen treatment improved motor function and stabilized disease activity in children with later-onset SMA.

doi:10.1212/WNL.0000000000007527

Neurology®

Evrysdi™ risdiplam 60 mg powder for oral solution

Not intrathecal administration but oral treatment at home

Tested in > 450 people with Type 1, 2, or 3 SMA from 2 months to 25 years old (also with severe scoliosis)

1) FIREFISH study (62 infants, 2-7 months of age with Type 1 SMA)

2) SUNFISH study (children and adults with type 2 or 3 SMA)

3) JEWELFISH study (people previously treated for SMA)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risdiplam in Type 1 Spinal Muscular Atrophy

Giovanni Baranello, M.D., Ph.D., Basil T. Darras, M.D., John W. Day, M.D., Ph.D., Nicolas Deconinck, M.D., Ph.D., Andrea Klein, M.D., Riccardo Masson, M.D., Eugenio Mercuri, M.D., Ph.D., Kristy Rose, Ph.D., Muna El-Khairi, Ph.D., Marianne Gerber, Ph.D., Ksenija Gorni, M.D., Ph.D., Omar Khwaja, M.D., Ph.D., Heidemarie Kletzl, Ph.D., Renata S. Scalco, M.D., Ph.D., Timothy Seabrook, Ph.D., Paulo Fontoura, M.D., Ph.D., and Laurent Servais, M.D., Ph.D., for the FIREFISH Working Group*